QM-Polarized Ligand Docking

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Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Table 1.1.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, and screen output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

QM-Polarized Ligand Docking

The QM-Polarized Ligand Docking protocol aims to improve the partial charges on the ligand atoms in a Glide docking run by replacing them with charges derived from quantum mechanical calculations on the ligand in the field of the receptor. In this way the polarization of the charges on the ligand by the receptor is accounted for, and redocking of the ligands with these new charges can result in improved docking accuracy. The protocol works by taking a small set of the best-scoring poses for each ligand, calculating charges using QSite, redocking each of these poses, and selecting the best poses from the set.

To run the QM-Polarized Ligand Docking protocol you must have an installed and licensed version of Glide 4.0 and QSite 4.0 (including Jaguar 6.5).

The QM-Polarized Ligand Docking Panel

In the QM-polarized ligand docking protocol, ligands are docked with Glide, then charges on the ligand induced by the protein are calculated with QSite, and a set of the best ligand poses are redocked. The QM-Polarized Ligand Docking panel collects the relevant controls for each part of the protocol, with judicious selection of defaults for options that are not presented in the panel. To open this panel, choose QM-Polarized Ligand Docking from the Applications menu on the main menu bar.

The panel is divided into two. In the upper section, the job options and input files for the sequence of jobs can be set. In the lower section, settings for each step of the process can be made. The foot of the panel has a row of action buttons.

A summary of the setup process is given below. The steps in the process are described in more detail in the following sections.

To set up a QM-polarized ligand docking calculation:

1. Set job options in the Job options section of the panel.
2. Set up the receptor grid in the Glide enclosing box section of the panel, or select an existing grid.
3. Select the ligands to be docked in the Ligands to be docked section.
4. Set the initial docking options in the Initial Glide docking section.
5. Select the level of the quantum mechanical treatment in QSite.

6. Enter the number of poses to keep for each ligand in the redocking of each of the poses selected for QM charge evaluation.
7. Select the energy parameter by which the final poses are scored.
8. Click Start.

When the job finishes, a pose viewer file is generated with the final selections. In addition, a *jobname*`.log` file is generated.

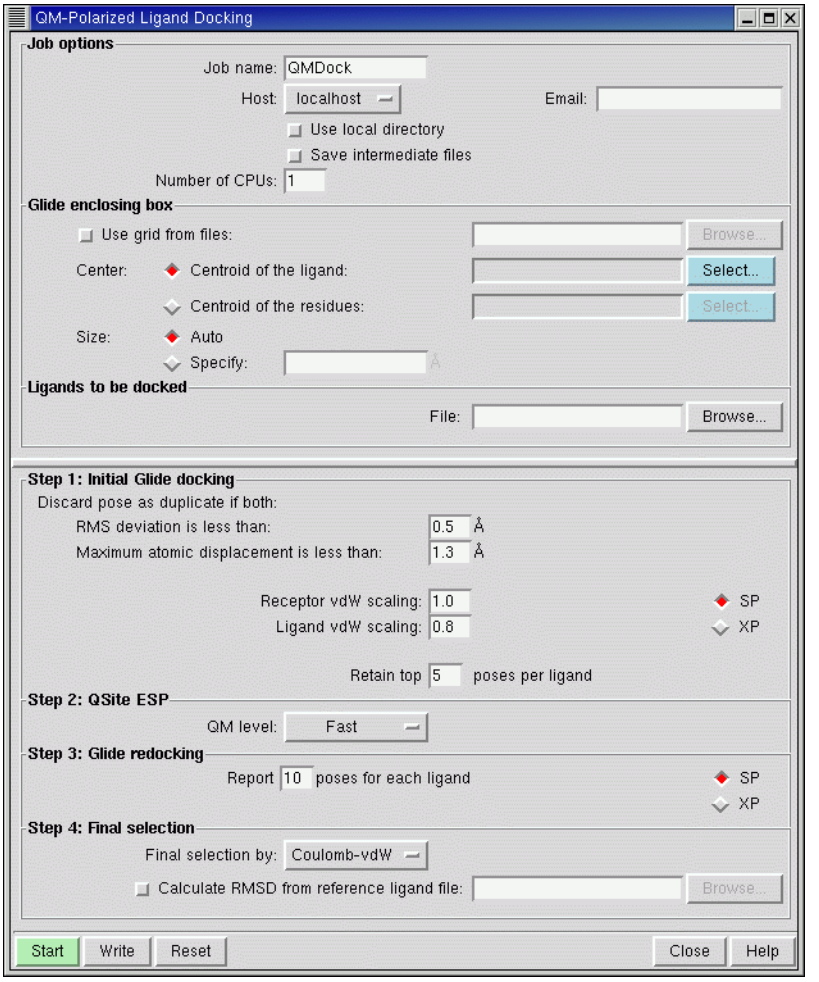

Figure 1.1. The QM-Polarized Ligand Docking ***panel.***

If you want to change any of the options for which controls are not provided in this panel, you can click Write, and the files for the calculation are written. You can then run the calculations from the command line, but you must run each application separately.

If you are docking a single ligand and want to calculate the RMSD of the resultant poses from a reference ligand, select Calculate RMSD from reference ligand file and specify a Maestro, SD, or PDB file that contains the reference ligand, which must have the same structure as the input ligand. The results are written to a *jobname*_rmsd.out file.

If you want to start the setup process again with the default options, click Reset.

Setting Job Options

The Job options section of the QM-Polarized Ligand Docking panel contains the usual controls for setting the job name and selecting a host that are found in the Start dialog box. There are no incorporation options: the results are written to the output file and a pose viewer file in the working directory.

In addition to the usual controls, there are several other controls for running the job:

- You can enter an email address in the Email text box if you want to be notified by email that the job has finished.
- You can select Use local directory to store all files including temporary files in the local directory, and you can select Save intermediate files to store the output of each stage in the protocol.
- You can run the job on multiple CPUs if the host is a multiprocessor host, by entering the appropriate number in the Number of CPUs text box. The ligands are divided between the CPUs, and each CPU runs the entire protocol for each of its ligands. Multiple CPUs are not used for QSite (Jaguar) parallel calculations.

Setting Up the Grid

The grid for the QM-polarized ligand docking job can be set up as part of the job, or it can be read from a previous Glide grid generation job. The QM-Polarized Ligand Docking panel offers a limited range of options for setting up the grid. If you want greater flexibility, you should set up the grid using the Glide Receptor Grid Generation panel, which is described in Chapter 6 of the *Glide User Manual*.

If you want to use an existing grid, select Use grid from file, and enter the name of the grid file in the text box, or click Browse and navigate to the grid file (.grd).

If you want to set up the grid as part of the job, you can specify the center and size of the enclosing box. All other parameters take their default values. To set up the grid, the receptor must be displayed in the Workspace, with or without the ligand. If a ligand is not displayed, you must define the center of the enclosing box in terms of receptor residues. The protein must be properly prepared for a Glide calculation. See Chapter 4 of the *Glide User Manual* for more information on protein preparation, and Chapter 6 of the *Glide User Manual* for more information on grid generation.

The options for the center of the enclosing box are:

- Centroid of the ligand—Center the enclosing box on the ligand centroid. The centroid is the mean position of the non-hydrogen atoms in the ligand. To select the ligand, click the Select button. The Atom Selection dialog box opens, in which you can select the atoms to define the ligand. The ASL expression for the atoms is displayed in the text box.
- Centroid of the residues—Center the enclosing box on a group of receptor residues. To select residues for the centroid, click the Select button. The Atom Selection dialog box opens, in which you can select the residues to define the centroid. The ASL expression for the residues is displayed in the text box.

The options for the size of the enclosing box are:

- Auto—automatically determine the size of the enclosing box. If the Center option is Centroid of the ligand, the enclosing box size is calculated automatically from the size of the ligand. If the Center option is Centroid of the residues, the enclosing box size is set to 26 Å on each side.
- Specify—set the size of the enclosing box. Enter the desired side length in the text box, in angstroms. The enclosing box has sides of equal length given by the value in the text box.

Selecting Ligands To Be Docked

The ligands to be docked must be properly prepared (for example, by using LigPrep) and must be in a Maestro, SD, or PDB file. Because the QSite step takes much more time than the Glide docking steps, you should restrict the number of ligands to a relatively small set, which might be the results of a previous docking run. To select the ligands, in the Ligands to be docked section, enter a file name in the text box, or click Browse and navigate to the file containing the ligands.

For more information on preparing ligands, see the *LigPrep User Manual*.

Setting Initial Glide Docking Parameters

The tasks in the Initial Glide docking section are to set parameters for the elimination of duplicate poses, scale the van der Waals radii if necessary, select the docking mode, and decide how many poses to keep per ligand. The defaults represent reasonable choices.

Thresholds for discarding duplicate poses

These two text boxes specify the thresholds for discarding a pose as a duplicate. Both thresholds must be met for a pose to be discarded. Specify the RMS deviation and the maximum atomic displacement thresholds in angstroms.

Van der Waals scaling text boxes

Specify scaling factors for the van der Waals terms for the receptor and the ligand in these two text boxes. For more information on the scaling, see Section 6.2.2 and Section 7.3.3 of the *Glide User Manual*.

Docking mode options

Select SP or XP docking mode. For more information on the docking modes, see the Glide Docking Settings Folder topic.

Retain top poses per ligand text box

Enter the number of poses to retain for the QSite ESP calculations. The QSite calculation is time-consuming, so only a small number of poses should be retained. The default value is 5, a value that has been optimized based on our research.

Selecting a QM Treatment Level

In the QSite ESP section, you can select a level of quantum-mechanical treatment of the ligand in the field of the receptor. The selection is a trade-off between speed and accuracy. The charges are calculated from the electrostatic potential energy surface of the ligand, which is generated from a single-point calculation using density functional theory for the QM region.

- Fast— Uses smaller basis sets and grids with the BLYP density functional.
- Medium— Uses larger basis sets and grids with the BLYP density functional.
- Accurate— Uses larger basis sets and grids with the B3LYP density functional.

Setting Glide Redocking Parameters

In the Glide redocking section, you can choose the docking mode (SP or XP) for redocking of the ligands with updated QM charges, and enter the number of poses to keep for each redocked ligand.

Specifying the Final Selection

In the Final selection section, you can specify how the poses are ranked and calculate an RMSD from a reference ligand.

The Final selection by option menu offers the choice of three quantities by which the poses are ranked: the Coulomb-vdW energy, the GlideScore, and Emodel. For a description of these quantities, see Chapter 3 of the *Glide User Manual*.

The Calculate RMSD from reference ligand file option allows you to calculate the RMSD of the various poses of the redocked ligand relative to a reference ligand which is read from file. Specify the path to the file, or click Browse to navigate to the file. The reference ligand must have the same structure (atom types and order) as the input ligand. The poses are listed in rank order with their RMSD values in the file *jobname*_`rmsd.out`. This option can only be used for single-ligand runs.

Citing QM-Polarized Ligand Docking in Publications

Schrödinger Suite 2006 QM-Polarized Ligand Docking protocol; Glide version 4.0, Schrödinger, LLC, New York, NY, 2005; Jaguar version 6.5, Schrödinger, LLC, New York, NY, 2005; QSite version 4.0, Schrödinger, LLC, New York, NY, 2005.

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the folder that is displayed in a panel, click the Help button in the panel. The Help panel is opened and a relevant help topic is displayed.
- For other information in the online help, open the Help panel and locate the topic by searching or by category. You can open the Help panel by choosing Help from the Help menu on the main menu bar or by pressing CTRL+H.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Glide User Manual*, for information on using Glide
- *Glide Quick Start Guide*, for Glide tutorials
- *QSite User Manual*, for information on using QSite
- *Maestro User Manual*, for detailed information on using Maestro
- Frequently Asked Questions pages on the Schrödinger Support Center

The manuals are also available in PDF format from the Schrödinger Support Center. Information on additions and corrections to the manuals is available from this web page.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail: help@schrodinger.com
USPS: 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information, most of which can be obtained by entering `$SCHRODINGER/machid` at a command prompt:

- All relevant user input and machine output
- Glide/QSite purchaser (company, research institution, or individual)
- Primary Glide/QSite user
- Computer platform type
- Operating system with version number
- QSite version number
- Glide version number
- Maestro version number
- mmshare version number

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